also specifically insert language for which proper antecedent basis exists. Claim 12 was amended to correct an editorial oversight. No new matter is added by amendment to claims 1, 2, 12 and 13.

Rejection of Claims 1-7 and 13 Under 35 U.S.C. § 112, Second Paragraph

Claim 1-7 and 13 were rejected under 35 U.S.C. § 112, second paragraph, as allegedly "being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention." Applicants respectfully overcome this rejection in light of the following amendments.

Claim 1 is amended to delete reference to "or functional equivalents."

Claim 2 is amended to delete reference to "or functional equivalents."

Claim 13 is amended to recite "polynucleotide" instead of "polynucleotides," as suggested by the Examiner.

In light of the amendment to claims 1, 2 and 13, Applicants request withdrawal of the rejection of original claims 1-7 and 13 under 35 U.S.C. § 112, second paragraph.

Rejection of Claims 1-13 Under 35 U.S.C. § 103(a)

Claims 1-13 were rejected under 35 U.S.C. § 103(a) as allegedly "being unpatentable over Cox et al (J. Virol. 67(9): 5664 (1993)) in view of applicants' admitted state of the prior art (e.g., instant application, page 32, lines 15-19)." The Examiner states that "[i]t would have been obvious for one of ordinary skill in the art to use any of the admittedly old HSV-2 DNA sequences in the method of Cox et al to elicit an immune response to HSV-2." Applicants respectfully disagree. Applicants maintain that the reference cited by the Examiner, in combination with Applicants' description of prior art, does not assure a reasonable expectation of successful immunization using a DNA-based vaccine approach to elicit neutralizing antibodies to HSV.

Cox et al. discloses DNA vaccination for protection from BHV. DNA vaccine technology was in its infancy when the present application was filed, and thus Applicants argue that a reasonable expectation of success in generating an immune response to HSV using DNA vaccination was not evident in light of Cox et al. Applicants show in the instant application that DNA vaccination encoding some HSV proteins is sufficient in protecting animals against lethal infection. In their discussion of experimental models of genetic immunization, Ertl and Xiang (1996, *Viral Immunol.* 9:1-9; attached hereto as Exhibit A) disclose that "although any antigens

can be delivered by genetic immunization, some proteins upon expression by plasmid vectors remain immunologically silent" (p. 2). Indeed, the instant application discloses that even though HSV protein ICP27 is known to generate a CTL response with ICP27-vaccinia recombinant virus, mice vaccinated with DNA encoding ICP27 alone did not provide protection from lethal HSV challenge (p. 21 of the specification, lines 3-8). This demonstrates that even among the array of HSV proteins with the potential of eliciting antibodies to the virus, not all of these proteins will be effective in eliciting such antibodies when introduced to the host as a polynucleotide. Thus, although Cox et al. discloses an instance of successful DNA vaccination, this does not ensure an expectation of success in producing neutralizing antibodies when vaccinating with any polynucleotide.

Applicants further maintain that even though BHV and HSV are related alpha viruses, it is crucial to recognize that these viruses are indeed different. Most obviously, BHV is a virus of cows; while HSV is a human virus. HSV primarily infects the genital mucosa and spreads mainly by sexual contact; while BHV primarily causes respiratory infections and is spread by droplet. Huemer et al. (1993, *Arch. Virol.* 130:353-364; attached hereto as Exhibit B) further establishes the differences between HSV and BHV by examining the species specificity of the interaction between glycoprotein C (gC) and third complement component (C3). Huemer et al. shows that HSV-1 gC preferentially binds human C3 when compared to C3 of different species, including porcine and cow. Similarly, BHV-1 gIII (the homologue of HSV-1 gC) preferentially binds bovine C3. These binding patterns correlate with the species tropism of infection, leading the authors to emphasize that "HSV-1 is a pathogen of humans but not of pigs and cows," and "BHV-1 causes disease of cows but not of pigs or humans" (p. 360, line 14 to p. 361, line 1). Applicants maintain that not only was the expectation of successful immunization with DNA vaccines minimal at the time of the claimed invention, but alleged support for efficacy of a DNA vaccine for disease A, caused by virus A in animal host A does not support efficacy of a DNA vaccine for disease B, caused by virus B in animal host B. In light of the above arguments, Applicants take the position that whatever motivation can be gleamed from the cited reference falls far short of instilling in one of skill in the art a reasonable expectation of success in practicing the claimed invention.

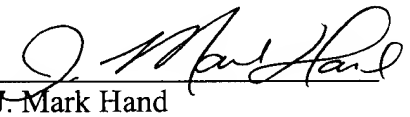
However, in addition to the discussion above and in order to solely speed prosecution of this application, Applicants submit with this response a 37 C.F.R. § 1.132 declaration (attached hereto as Exhibit C1 and C2)[1], made by the inventors of the instant application, showing that the

[1] The executed Declaration of Robert D. Keys was not available as of the time this Amendment and attachments were deposited for mailing under 37 C.F.R. 1.8(a). Upon receipt, this executed Declaration will be hand delivered to the Examiner.

claimed invention was conceived and reduced to practice prior to the publication of Cox et al. The declaration documents Applicants' experimental process in developing and testing an HSV polynucleotide vaccine described in the application. Mice immunized with plasmid DNA encoding HSV-2 glycoprotein D (gD) were challenged through IP injections with HSV virus and observed for illness/death. A graph described in the declaration, and attached thereto, summarizes the results showing that mice immunized with the polynucleotide were protected against HSV infection. This graph is reproduced in the instant application as Figure 4. Applicants submit this declaration, and the accompanying data, as evidence that the method of using HSV plasmid DNA as a polynucleotide vaccine to protect against HSV infection was novel and nonobvious at time the claimed invention was made.

In view of the amendments and comments herein, Applicants respectfully take the position that all claims are in proper form for allowance and earnestly solicit a favorable action on the merits. The Examiner is invited to contact the undersigned attorney if clarification is required on any aspect of this response, or if any of the claims are considered to require further amendment to be placed in condition for allowance after entry of this Amendment.

Respectfully submitted,

By 

J. Mark Hand
Reg. No. 36,545
Attorney for Applicant

MERCK & CO., INC.
P.O. Box 2000
Rahway, New Jersey 07065-0907
(732) 594-3905

Date: April 2, 2003

MARKED-UP VERSION OF APPLICATION AS AMENDED HEREIN

IN THE CLAIMS:

Claims 1, 2, 12 and 13 were amended as follows:

1(Amended). A polynucleotide which induces anti-HSV antibodies or protective immune responses upon introduction into vertebrate tissue, wherein said polynucleotide comprises at least one gene encoding at least one HSV protein or truncated protein [or functional equivalents thereof], said gene or genes being operably linked to a transcriptional promoter.

2(Amended). The polynucleotide of Claim 1, wherein said gene encodes an HSV protein selected from a group consisting of gB, gC, gD, gH, gL, ICP27 and truncated gB [functional equivalents thereof].

12(Amended). A method for inducing immune responses in a vertebrate against HSV epitopes which comprises introducing the vaccine according to Claim 11 into a tissue.

13(Amended). A vaccine for inducing immune responses against HSV which comprises the polynucleotide [polynucleotides] of Claim 11 and a pharmaceutically acceptable carrier.